REMARKS/ARGUMENTS

We note that the Examiner did not enter the Amendment After Final that was filed on March 3, 2003. Consequently, the same amendments are being submitted herewith in addition to several new amendments. By the present amendment, claims 4, 5, 7-10, 12-14, 18-20, 24-28, 41, 43 and 44 are being amended and claims 2-3, 11, 17, 21-23, 31-40 and 42 are being deleted rendering claims 1, 4-10, 12-16, 18-20, 24-30, 41, 43 and 44 pending in the application. The amendments to the clams have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further continuation, continuation-in-part or divisional application.

Specification/Informalities

The Examiner has objected to the title of the invention and suggests a new title. In response, Applicant has adopted the Examiner's suggestion.

Claim Objections

The Examiner has objected to claim 27 as the sequence identifier was improper. In response, claim 27 has been corrected.

35 USC §101

The Examiner has rejected claim 42 under 35 USC §101 alleging that the claim is not supported by a specific and substantial asserted utility or a well-established utility. In response, claim 42 has been amended without prejudice and in order to advance prosecution of the application.

35 USC §112, Second Paragraph

The Examiner has objected to claims 4, 5, 7-14, 19, 24-27, 43 and 44 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In response, these claims have been amended in order to replace the article "a" with the article "the" as requested by the Examiner.

In view of the foregoing, we respectfully request that all of the objections under 35 USC §112, second paragraph be withdrawn.

35 USC §112, First Paragraph

The Examiner has objected to claim 42 under 35 USC §112, first paragraph. As mentioned above, claim 42 has been deleted by the present amendment.

The Examiner has objected to claims 7, 11, 12, 17 and 18 under 35 USC §112, first paragraph, as lacking enablement. In particular, the Examiner alleges that claim 7 is only enabled by a pH value of 2 to about 7. In response, claim 7 has been amended to specify that the pH is between 2 to 7. The Examiner also alleges that the in vivo conditions are only enabled for body fluids that consist of the milk, the stomach, or the gut but not the blood or kidneys. In response, claims 12 and 18 have been amended accordingly and previous claims 11 and 17 have been deleted.

In view of the foregoing, we respectfully request that all of the objections under 35 USC §112, first paragraph be withdrawn.

35 USC §102

The Examiner has objected to claims 20, 25, 26, 28, 29, 30, 41, 43 and 44 under 35 USC §102(b) as being anticipated by Hiramatsu et al. (*Appl Environ Microbiol* (1990) 56:2125-2132, hereinafter referred to as "Hiramatsu et al. (1990)"). We respectfully disagree with the Examiner for the reasons that follow.

Hiramatsu (1990) teaches only one vector JGH2 that contains part of a pro-sequence of *Mucor Pusillus* Rennin (MPR). The JGH2 vector comprises the full length pre-sequence and only five amino acids of the pro-sequence fused to human growth hormone via a 3 amino acid linker sequence. The full length pro-sequence contains 40 amino acids and one of skill in the art would not interpret a sequence containing the five N-terminal residues of a pro-peptide sequence as "a chymosin pro-peptide" as recited in the

present claims. Consequently, we respectfully submit that the claims are not anticipated by Hiramatsu et al. (1990).

In view of the foregoing, we respectfully request that the objection to the claims under 35 USC §102 be withdrawn.

35 USC §103

The Examiner has objected to claims 1, 4, 6-10, 13-16 and 19 under 35 USC 103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu (*J Biol Chem* (1989) 264:16862-16866; hereinafter referred to as "Hiramatsu et al. (1989)"). We respectfully disagree with the Examiner for the reasons that follow.

As mentioned above, Hiramatsu (1990) teaches only one vector JGH2 that contains part of a pro-sequence of *Mucor Pusillus* Rennin (MPR). The JGH2 vector comprises the full length pre-sequence and only five amino acids of the pro-sequence fused to human growth hormone via a 3 amino acid linker sequence. Importantly, Hiramatsu (1990) reports that they did not get efficient cleavage of the pro-sequence from the hGC sequence with only part of the pro-sequence. In particular, they found that cleavage had occurred at the junction of the pre- and pro-sequences thus yielding an hGC sequence with the pro-sequence still N-terminally attached thereto. They suggest various strategies to overcome these difficulties such as including an artificial cleavage site (such as one recognized by blood coagulation factor Xa) between the pro-sequence and the heterologous protein sequence. Hiramatsu (1990) in no way discloses or remotely suggests that a pro-sequence can be directly fused to a heterologous protein which results in efficient cleavage. Therefore, Hiramatsu (1990) teaches away from the present invention as it recommends that an artificial cleavage site is inserted in the chimeric construct.

The deficiencies in Hiramatsu (1990) are no way remedied by Hiramatsu (1989). Hiramatsu (1989) is not at all concerned with the preparation of heterologous proteins. Hiramatsu (1989) describes the expression of a *Mucor* pre-pro-chymosin polypeptide in

Saccharomyces. Evaluating the expression of pre-pro-chymosin and a mutated form of the enzyme (point mutation at active site) in wildtype Saccharomyces and a mutant Saccharomyces strain lacking a protease, the authors determine that the Mucor chymosin is secreted in the form of a preproenzyme which is then predominantly processed autocatalytically and to a lesser extent by yeast proteases. This art in no way teaches or suggests to link a pro-enzyme to a heterologous protein.

We disagree with the Examiner that it would have been obvious to one of ordinary skill in the art to combine the teachings of Hiramatsu (1990) and Hiramatsu (1989) to replace the pro-peptide fragment with the full length pro-peptide sequence that includes the proper cleavage site. If such a solution would have been obvious, then we respectfully submit that it would have been discussed in the conclusion of Hiramatsu (1990). In fact, as mentioned above, Hiramatsu (1990) teaches away from the present invention and suggests another solution to overcome the cleavage problem by the introduction of an artificial cleavage site. Even if one of skill in the art was motivated to use a larger portion of the pro-sequence, there would be no guarantee of success of efficient cleavage as the present inventors have demonstrated.

The inventiveness of the present invention is further supported by Nomura et al. (*Biosci. Biotech. Biochem.* 59(3), 382-387, 1995). Nomura et al. teaches that the entire rennin gene is needed for efficient secretion of the heterologous protein apolipoprotein E. Consequently, at the time of the invention, one of skill in the art would not predict that the method of the present invention, wherein only a pro-peptide sequence is used, would be efficient for the production and efficient cleavage of a heterologous protein.

The Examiner has objected to claims 5 and 24 under 35 USC §103(a) as being unpatentable over Hiramatsu et al. (1990) in view of Hiramatsu (1989) as applied to claims 1, 4, 6-10, 13-16 and 19 above, and further in view of Fine et al. (*Gen Comp Endocrinol* (1993) 89:51-61). We respectfully disagree with the Examiner for the reasons that follow.

Claims 5 and 24 relate to a specific embodiment wherein the heterologous protein is carp growth hormone. Claim 5 depends from claim 1 and claim 24 depends from claim 20. We submit that claims 1 and 20 are novel and inventive over Hiramatsu (1990) and Hiramatsu (1989) for the reasons stated above. The deficiencies in the Hiramatsu references are not remedied by Fine which is a reference that describes expression of Carp Growth Hormone (cGH) in *E.coli*, purification of cGH from *E.coli*, *in vitro* (using lymphoma and preadipocyte cells) and *in vivo* (evaluating growth rate in fish injected with the purified protein) characterization of cGH. Again, this art in no way teaches or suggests to link a pro-enzyme to a heterologous protein. Since Applicant is claiming the production of carp growth hormone by a novel and inventive method or in a novel and inventive nucleic acid construct, we submit that these claims are patentable over the cited references.

In view of the foregoing, we respectfully request that all of the objections under 35 USC §103 be withdrawn.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to our Deposit Account No. 02-2095.

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Micheline Gravelle at 416-957-1682 at his convenience.

Respectfully submitted,

BERESKIN & PARR

By M. Gravelle
Micheline Gravelle
Reg. No. 40,261

Bereskin & Parr
Box 401, 40 King Street West
Toronto, Ontario
Canada M5H 3Y2
Tel: 416-957-1682
Fax: 416-361-1398

Attachments